Fact Sheet for Health Care Providers: Interpreting Results from the Aptima® Zika Virus Assay

June 17, 2016

Dear Health Care Provider:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the Aptima® Zika Virus assay on the Panther System instrument for the *in vitro* qualitative detection of RNA from Zika virus in human serum and plasma specimens. Testing should be conducted only on specimens from individuals meeting Centers for Disease Control and Prevention (CDC) Zika clinical and/or epidemiological criteria for testing (http://www.cdc.gov/zika/hc-providers/index.html) by laboratories in the U.S. that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories.

FDA issued this EUA based on data submitted by Hologic, Inc. to FDA, and on the U.S. Secretary of Health and Human Services' (HHS) declaration that circumstances exist to justify the emergency use of *in vitro* diagnostic tests for the detection of Zika virus and/or diagnosis of Zika virus infection. This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

The information in this Fact Sheet is to inform you of the significant known and potential risks and benefits of the emergency use of the Aptima® Zika Virus assay. For more information on this EUA, please see FDA's website at: http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm.

Why is this test needed at this time?
As of May 26, 2016, active Zika virus transmission is occurring in 40 countries and territories in the Americas, 8 countries and territories in Oceania/Pacific Islands and 1 country in Africa (http://www.cdc.gov/zika/geo/active-countries.html). Among cases identified in 2015-16, Zika virus transmission has occurred primarily through the bite of infected *Aedes* species mosquitoes. There is increasing evidence that Zika virus can also be transmitted from mother to fetus during pregnancy and through sexual transmission from infected males to their sexual partners.

As of June 08, 2016, there have been more than 691 confirmed cases of Zika virus infection in the continental United States. All of these individuals have either a recent travel history to areas with ongoing transmission or an epidemiologic link with an individual with such a travel history (i.e., through maternal-fetal or sexual transmission). Public health officials have determined that Zika virus poses a potential public health emergency.

At this time, there are no FDA approved/cleared tests available that can detect Zika virus in clinical specimens in the U.S. Hologic, Inc. has developed the Aptima® Zika Virus assay to detect evidence of Zika virus infection. Current information on Zika virus infection for health care providers, including case definitions, is available at http://www.cdc.gov/zika/hc-providers/index.html. All information and guidelines, including those on Zika virus laboratory testing, may change as more data are gathered on this virus. Please check CDC's Zika virus website regularly for the most current information (http://www.cdc.gov/zika/index.html).

If Zika virus infection is suspected based on current clinical and/or epidemiological criteria recommended by public health authorities, the Aptima® Zika Virus assay may be ordered. As chikungunya virus infection and dengue virus infection can have early symptoms resembling those of Zika virus infection, and co-infection with these viruses is possible, in addition to testing for Zika virus, testing should be considered for chikungunya and dengue. Please contact your state or local health department to facilitate testing. Zika virus RNA is typically detectable in serum for approximately 7 days following onset of symptoms.

The results should be used in conjunction with clinical signs and symptoms, epidemiological information and travel history to diagnose Zika virus infection. This test is authorized for use with serum and plasma.

As of June 17, 2016, serum is the primary diagnostic specimen and should be the priority specimen for collection and testing. Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device.

What are the symptoms of Zika virus infection?
Most people with Zika virus infection are asymptomatic. Symptomatic patients typically experience a mild illness characterized by fever, joint pain, rash, or conjunctivitis. Clinical illness is usually self-limited and lasts a week or less. Not all symptomatic patients report all of these clinical findings, and Zika manifestations overlap significantly with those seen in other viral infections. The incubation period is unclear, but likely to be several days. Symptoms generally resolve on their own within a week.

Reports from Brazil, a country with a large number of Zika virus cases, indicate an association between Zika virus infection in pregnant women and increased incidence of microcephaly (a birth defect characterized by small head size and impaired cranial and neural development in neonates) as well as central nervous system injury, placental insufficiency, fetal growth restriction, and fetal death.

Mounting evidence in the literature increasingly supports a causal relationship between prenatal Zika virus infection and microcephaly and other serious brain anomalies in fetuses and babies.[1,2] However, limited information is available currently about the spectrum of defects caused by prenatal Zika virus infection, the degree of relative and absolute risks of adverse outcomes among fetuses whose mothers were infected at

different times during pregnancy, and factors that might affect a woman's risk of adverse pregnancy or birth outcomes.

There are also reports of a possible association between Zika virus infection and increased incidence of Guillain-Barré syndrome.

Zika infection shares epidemiologic and clinical features with chikungunya, dengue, and other infections. Molecular and/or serologic testing for Zika infection may be useful to diagnose the etiology of a given (usually travel-related) illness and guide further testing and management as needed.

When should the Aptima® Zika Virus Assay test be performed?
Zika virus RNA may be detected in serum for approximately 4-7 days following onset of symptoms; thus the optimum time to perform serum RNA testing is during the first week after the onset of clinical illness. For patients who are 2-12 weeks post-symptom onset, serologic testing should be considered. Test results should be used in conjunction with clinical signs and symptoms, epidemiological information and relevant travel history to diagnose Zika virus infection.

Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device. Sera should be collected in serum separator tubes and centrifuged after collection to reduce the likelihood of hemolysis.

What does it mean if the specimen tests positive for Zika virus RNA?
A positive test result for Zika Virus RNA indicates that RNA from Zika virus was detected in the patient's sample. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis and patient management decisions. For guidelines on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

The Aptima® Zika Virus assay has been designed to minimize the likelihood of false positive test results. Cross-reactivity with other viruses, including chikungunya and other flaviviruses such as dengue and West Nile, is not expected. However, in the event of a false positive result, risks to patients could include any or all of the following: the impaired ability to detect and receive appropriate medical care for the true infection causing the symptoms, in the case of pregnant women, an unnecessary increase in the monitoring of a woman's pregnancy, or other unintended adverse effects.

All positive Zika virus test results should be reported to your local and state health authorities.

It should be emphasized that the identification of Zika virus infection in a pregnant woman does not provide any definitive information about the state of health of the fetus. Many questions remain about the association between Zika virus infection in a mother and the impact to the fetus, and the impact of factors such as timing, likelihood,

relevance of symptomatic versus asymptomatic infection. Detection of Zika virus infection in the mother does not mean there is definite harm to the fetus.

What does it mean if the specimen tests negative for Zika virus RNA?
A negative test for Zika virus RNA in the specimen means that RNA from Zika virus is not present in the specimen above the assay's limit of detection.

Given the reported transient, low-level viremia in many patients diagnosed with Zika virus infection, a negative result, especially if testing is performed after 7 days of symptom onset, does not exclude the possibility of Zika virus infection. Zika virus RNA negative results should not be used as the sole basis for treatment or other patient management decisions. The possibility of a false negative result should be considered if a patient's travel history and/or clinical illness raise suspicion of Zika infection. Such patients should be considered for serologic testing which is best performed 2-12 weeks after symptoms onset.

Further information on Zika virus infection for health care providers is available at http://www.cdc.gov/zika/hc-providers/index.html.

Reporting Adverse Events
You should report adverse events, including problems with test performance or results, to MedWatch at http://www.fda.gov/medwatch, by submitting a MedWatch Form 3500 (available at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=professional.reporting1) or by calling 1-800-FDA-1088.

Pregnant patients should receive the *Fact Sheet for Pregnant Women: Understanding Results from the* Aptima® Zika Virus Assay.

Give all other patients the *Fact Sheet for Patients: Understanding Results from the* Aptima® Zika Virus Assay.

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Any significant new findings that negatively impact the performance of the test and that are observed during the course of the emergency use of the Aptima® Zika Virus assay will be made available at http://www.hologic.com/.

References

1) Rasmussen, S.A., Jamieson, D.J., Honein, M.A., Petersen, L.R. Zika Virus and Birth Defects – Reviewing the Evidence for Causality. New England Journal of Medicine, April 12, 2016. DOI: 10.1056/NEJMsr1604338.
2) CDC Website - http://www.cdc.gov/zika/